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Review

SH3 domain ligand binding: What's the consensus and where's the specificity?

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ABSTRACT

An increasing number of SH3 domain–ligand interactions continue to be described that involve the conserved peptide-binding surface of SH3, but structurally deviate substantially from canonical docking of consensus motif-containing SH3 ligands. Indeed, it appears that that the relative frequency and importance of these types of interactions may have been underestimated. Instead of atypical, we propose referring to such peptides as type I or II (depending on the binding orientation) non-consensus ligands. Here we discuss the structural basis of non-consensus SH3 ligand binding and the dominant role of the SH3 domain specificity zone in selective target recognition, and review some of the best-characterized examples of such interactions.

1. Introduction

SH3 domain is a small protein interaction module composed of a β-sandwich consisting of five strands connected by three loops and a short 3_{10} helix (Fig. 1). The pioneering early studies defined the ligand sequence PxxP as the minimal consensus target site for SH3 domain binding, and revealed how the PxxP motif is accommodated by two distinct xP dipeptide-binding pockets on the SH3 surface [1,2]. Moreover, it was found that such PxxP motif-containing peptides could be docked in two opposite orientations defined by the relative positioning of a positively charged residue (+xxPxxP or xPxxPx+) interacting with a negatively charged third cleft on the SH3 peptide-binding surface [3,4]. This third cleft was named the specificity pocket. Recognition of these Class I and Class II consensus SH3 binding motifs has since helped the identification of the interaction partners for many SH3 domains, and dominated the thinking in this field.

However, an increasing number of divergent SH3 domain target peptides, often referred to as atypical binding motifs, have been identified. Thus, it would probably be more appropriate to call such peptides non-consensus ligands, and to restrict the term atypical for the less common and fundamentally different interactions that involve entirely different surfaces on the SH3 domain (for examples, see [5,6]. Of note, excluding interactions involving additional tertiary contacts (e.g. Hck-SH3/Nef binding [7]), SH3/ligand complexes that show unusually strong affinity or distinct selectivity are usually, if not always, based on a non-consensus binding motif.

Unlike the canonical PxxP motif-based ligands, peptides containing non-consensus SH3 binding motifs do not always adopt a polyproline type-II (PPII) helical conformation, and may not occupy both xP-binding pockets of the SH3 domain (see Figs. 2 and 3). On the other hand, a characteristic feature of the non-consensus motifs is their extensive use of contacts with the SH3 surface that typically contains the negatively charged specificity pocket (see Figs. 2 and 4). Compared to the orientation-defining salt bridges provided by the specificity pocket upon Class I and II consensus binding, elaborate sets of contacts with side chain atoms from several residues in non-consensus ligands can provide significant additional affinity and specificity to these interactions. Indeed, the role of such contacts can dominate over those involving the xP-binding pocket interface of the SH3 domain.

The SH3 surface that contributes to these affinity/specificity-determining interactions is formed by a shallow valley above the β3 and β4 strands, flanked by the far end of strand β2/n-Src loop and the tip of RT loop (see Fig. 1). In many SH3 domains this surface consists of more than one distinct subpocket, which together with, or in many cases instead of, a canonical acidic pocket accommodate ligand residues located N- or C-terminally (in type I or II binding, respectively) of the xP-pocket-contacting region of the peptide (see peptide illustrations in Fig. 2). Because of its structural complexity and coverage of a large SH3 surface area, we prefer to use the term specificity zone to make a clear distinction to the traditional concept of a specificity pocket.

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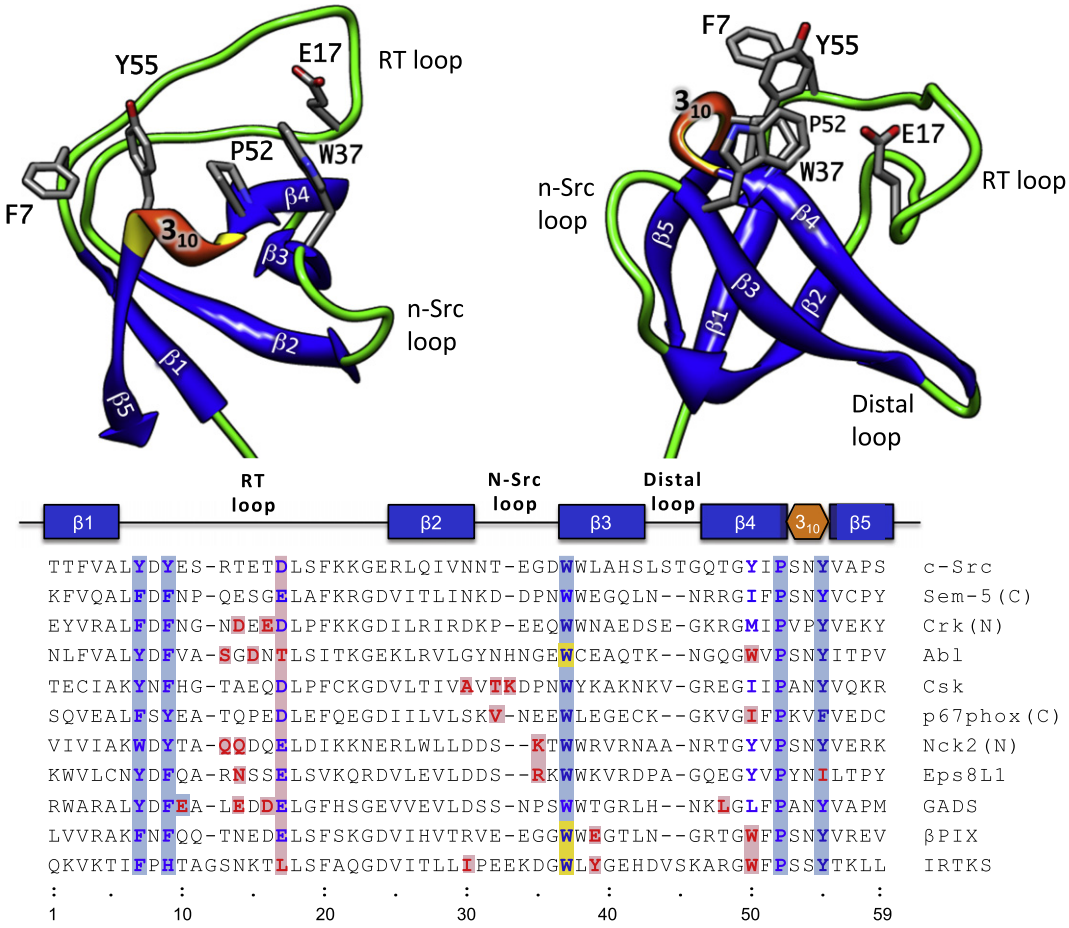


Fig. 1. Structural organization of the SH3 domain. Two ribbon models of a typical SH3 domain based on the crystal structure of Sem-5 SH3 are shown above an alignment of the amino acid sequences of the SH3 domains discussed here. The secondary structure elements of the SH3 fold are indicated above the sequences, and the numbering used for all SH3 domains in this paper is shown below the alignment. Expect for the *Caenorhabditis elegans* Sem-5, all sequences are of human origin. Shown in the Sem-5 structures as stick models are the side chains of the key residues that form the two conserved xP pockets (F7 + Y55 and W37 + P52) and the canonical acidic "specificity pocket" (E17). The most conserved ligand binding residues are also shown in blue in the alignment, whereas non-conserved residues providing distinct specificity for a given SH3 domain are shown in red. In addition, these residues are highlighted in different colors to indicate whether they participate in forming the xP pockets (light blue background), specificity zone (pink background), or both (yellow background).

The divergent strategies for combinatorial use of the xP pocket region and the specificity zone exhibited by different consensus or non-consensus ligands are illustrated in Fig. 2. Remarkably, common sets of molecular contacts with the SH3 specificity zone have evolved as modules that can appear in peptides containing a canonical PPII-helical PxxP motif as well as in peptides that interact with the SH3 xP-pocket region via other strategies.

A striking example of this is provided by the RxxK motif of the HPK1 and SLP-76 peptides that docks to the specificity zone of GADS SH3 domain in a similar manner, despite completely different modes of GADS xP-pocket surface recognition by these peptides [12–14]. On the other hand, even in the case of a single ligand peptide, the modes of xP pocket and specificity zone recognition can differ between two SH3 domains. This is clearly exemplified by binding of the aminoterminal SH3 domain of Nck and the Eps8L1 SH3 domain to CD3ε [15,16,21]. In both complexes much of the specificity and affinity of binding is provided by an interaction of a DY motif in the ligand with the SH3 specificity zone, whereas only Nck SH3 binding involves canonical accommodation of the CD3ε peptide as a PPII ligand on the xP pocket surface of the SH3 domain.

The binding determinants in the ligands that interact with the SH3 specificity zone can be quite complex and adopt distinct secondary structures. Presentation of such specificity determinants in the context of a 3_{10} helix can be observed in many cases, including the indicated high-affinity interactions of GADS [12–14], Csk [10], and βPIX SH3 [18–20] domains with their non-consensus ligands, whereas the remarkable binding strength (24 nM) of the carboxyterminal SH3 domain of p67phox with a proline-rich region of p47phox (another subunit of the NADPH oxidase) depends on an interaction between a helix-turn-helix structure in the p47phox ligand with the specificity zone of the p67phox SH3 domain [11]. Some, but not all of these interactions are complemented by canonical ionic interactions between a basic residue in the ligand an acidic pocket in the specificity zone of the SH3 domain (see Fig. 2).

Interestingly, the PPII helical conformation is not restricted to the xP-pocket region contacts by the ligands, but is also utilized for contacts with the specificity zone [20,21]. An extreme case of this is the complex between the IRTKS SH3 domain and its ligand $EspF_U$. This bacterial peptide contains a typical PPII-helical PxxP motif to interact with the xP pocket region of IRTKS SH3 as a Class I ligand, but exploits a unique strategy for interacting with the specificity zone. The specificity zone of IRTKS SH3 contains two hydrophobic clefts, which resemble the xP pockets and accommodate the aminoterminal part of the $EspF_U$ peptide in a manner that phenocopies a bona fide PPII-helical PxxP consensus peptide interaction [21].

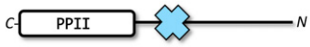
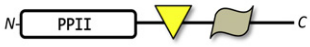
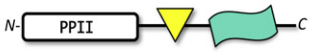
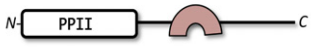
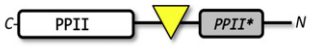
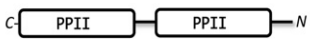
SH3	Ligand	Orientation	Ligand architecture	PDB entry	Ref.
e.g. Src	Class I or II consensus +xΦPxxP or xPxΦPx+	+/-		1RLQ 1SEM	[3, 4]
Crk(N)	C3G PPPALPPKKR	-		1CKA	[8]
Abl	p41 APSYSPPPPP	+		1BBZ	[9]
Csk	PEP PPPLPERTPESFIV	-		1JEG	[10]
p67phox(C)	p47phox PQPAVPPRPSADLILNRCSESTKRKLA	-		1K4U	[11]
GADS	HPK1 PPVLPPRKEK	-		1UTI	[12]
GADS	SLP-1 APSIDRSTKP	-		1OEB 1H3H	[13, 14]
Nck(N)	CD3ε PPPVPNPDYEPIR	-		2JXB 2JW4	[15, 16]
Eps8L1	CD3ε PPPVPNPDYEPIR	-		2ROL	[17]
βPIX	PAK PPPVIAPRPEHTKS	-		1ZSG 2G6F	[18, 19]
βPIX	AIP4 PSRPPRPSRPPPPTP	+		2P4R	[20]
IRTKS	$EspF_U$ IPPAPNWPAPTPP	+		2KXC	[21]

Fig. 2. Diverse strategies for SH3 ligand binding. Peptide conformations observed in a selected set of informative SH3 / ligand structures [3,4,8–21] are schematically shown together with key data on these interactions. The letters N and C are shown in parentheses after the name of proteins containing two SH3 domains to indicate whether the amino- or carboxyterminal SH3 is meant. The symbols Φ and Ω refer to hydrophobic and aromatic amino acid residues, respectively, whereas "+" is a positively charged residue (Arg or Lys), and x is any amino acid. Amino acid sequences of the relevant regions of the ligands are shown under the origin of these peptides. The relative orientation of the peptides in the SH3/ligand complexes is indicated by a plus (+) or a minus (−), and also by N and C marking the amino- and carboxytermini of the schematically illustrated ligand peptides. Since the majority of ligands included in the figure bind to their cognate SH3 domains as Class II ligands, we have chosen to depict the N-termini of such minus-orientation peptides as pointing to the left and their C-termini pointing to the right. When a peptide is interacting with the SH3 xP pocket surface as a typical PPII-helical, the corresponding xPxxP sequence is underlined in the sequence, and depicted in the peptide illustrations as a rounded white box marked PPII. Of note, the $EspF_U$ peptide is using an identical PPII structure also for its interaction with the specificity zone of the IRTKS SH3 domain. However, in this case the first xP pocket in the specificity zone is dedicated for binding an IP-dipeptide, thus providing specificity for this high affinity (500 nM) interaction. On the other hand, some ligands do not form any PPII helix, and instead interact with the SH3 xP-pocket via very different strategies. When the complex involves an interaction of a canonical positively charged residue of the ligand with an acidic pocket in the specificity zone of the SH3 domain, this residue has been colored red in the peptide sequence, and is indicated as a yellow/orange triangle in the peptide illustration. The orange triangle denotes the special case of the aminoterminal SH3 of the Crk/CrkL proteins. As revealed by the Crk/C3G complex structure these SH3 domains specifically select Class II ligands with a lysine as the positively charged consensus residue, which they coordinate in an unusual and tight manner by a set of three acidic SH3 residues [8]. The other residues in the ligand peptides that make key contacts with the SH3 specificity zone are colored green, and the structural elements presenting these residues are marked as various colored symbols in the peptide drawings.

Although the specificity zone is critical in providing distinct selectivity for SH3 interactions the xP pocket surface can also contribute specificity for binding. For example, the positioning of the highly conserved W37 residue is slightly different in SH3 domains complexed with Class I vs. II consensus ligands. Depending on the type of residue at position 55 this movement of W37 may be hindered, thereby allowing binding only to Class II peptides or to a subset of Class I ligands presenting Leu-Pro dipeptides to the SH3 xP pockets [24]. Examples of more distinguishing contacts with the xP pocket surface can be observed with SH3 ligands that do not contain PPII helical conformation, such as the complex involving the βPIX SH3 domain and its target peptide in p21-activated kinase-1 [18] and -2 [19]. Although SH3 domains like GADS (see Fig. 3) or Fyn [25] may bind both canonical PxxP ligands as well as non-PPII helical peptides, the anatomy of the xP pockets can favor one of these. As explained in more detail in the legend for Fig. 3, this is the case with the SH3 domains of Eps8L1 and GADS, which prefer non-PPII ligands because of their unusual amino acid residues in certain conserved xP-pocket-forming positions.

Other informative examples of n-Src loop residue modifications that contribute to ligand-specific contacts at the specificity zone are provided by the Csk SH3 in complex with PEP-3BP1 [10] and the C-terminal SH3 domain of $p67^{phox}$ in complex with $p47^{phox}$ [11]. In both cases, the ligand peptides bind in the minus-orientation, and canonical contacts with the SH3 xP pockets and an acidic pocket in the specificity zone. However, for additional contacts with the specificity zone, both peptides form a helical structure, although the exact roles of these secondary structures are quite different. The PEP-3BP1 establishes a 3_{10} helix presenting a hydrophobic isoleucine residue that clamps around a finger in the n-Src loop formed by K33 of Csk SH3. This interaction is complemented by a valine in PEP-3BP1 that inserts into a hydrophobic cavity (circled in yellow) in the specificity zone of Csk SH3 formed by A30 and T32. In the case of $p67^{phox}$–$p47^{phox}$ complex, the

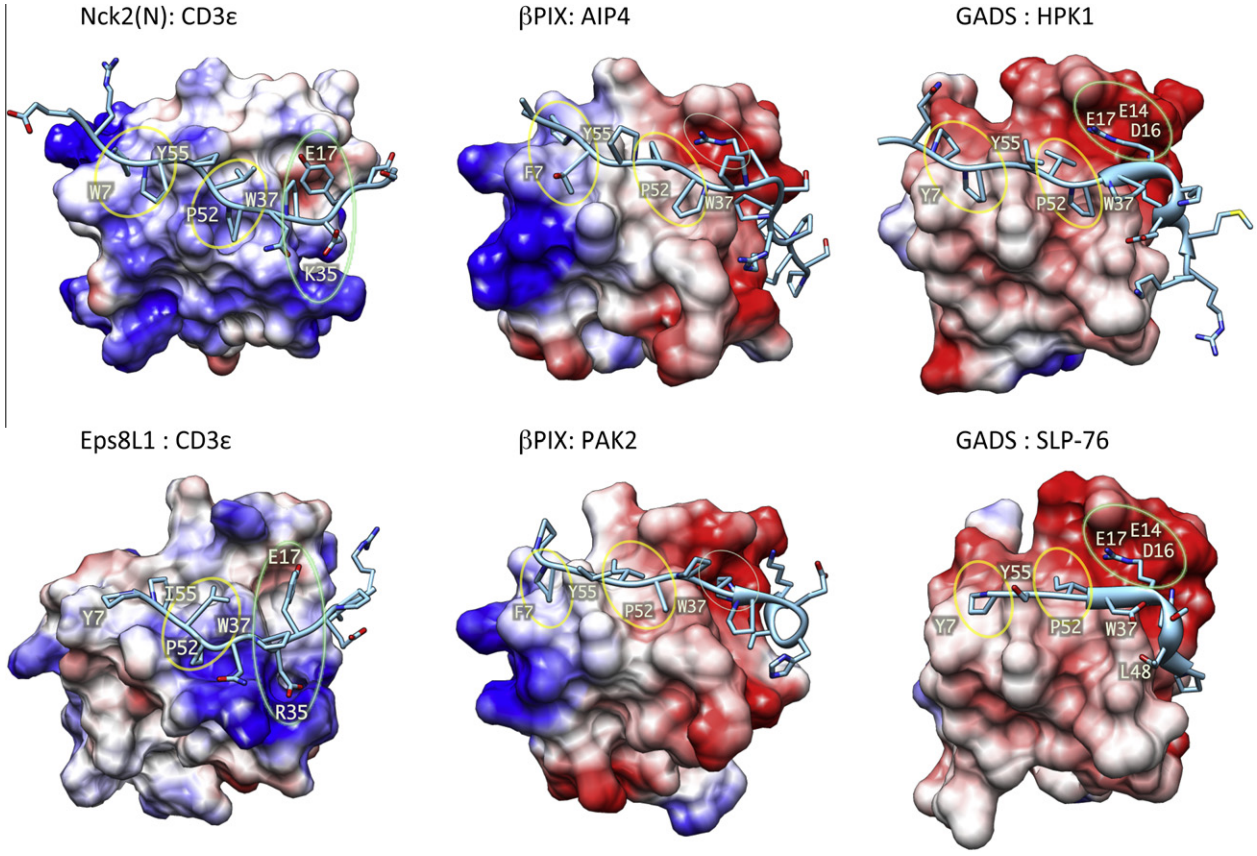


Fig. 3. Examples of combinatorial strategies used by ligands to interact with the xP pockets and specificity zone surfaces of SH3 domains. SH3 domains are shown using Coulombic surface presentation, whereas their ligands are shown with a stick model. The key residues in the SH3 domains involved in providing specificity for these interactions are indicated using the residues numbering shown in Fig. 1. Hydrophobic xP pockets are circled in yellow, whereas the relevant surfaces of the specificity zone are circled in green. The N-terminal SH3 of Nck2 [15] and the SH3 of Eps8L1 [17] are shown in complex with a peptide from the cytoplasmic tail of CD3ε. The SH3 domains of the Eps8 family members as well as the N-terminal SH3 domains of Nck1 and Nck2 bind PxxDY motifs [22,23]. The key interactions, determining the specificity towards PxxDY ligands are established between the aspartate residue of the PxxDY motif and a basic SH3 residue in position 35 within the n-Src loop, and between the PxxDY tyrosine and E17 in an acidic cleft corresponding to the specificity pocket of archetypal SH3 domains. However, the CD3ε peptide is in a PPII conformation when bound to Nck, but in an extended conformation when bound to Eps8L1. Explaining this, the SH3 of Eps8L1 (like the rest of the Eps8 family) has an isoleucine instead of tyrosine in the conserved position 55, which renders the shape of the first hydrophobic slot different and non-optimal for accommodation of classical XP dipeptide. For this reason, N-terminal SH3 domains of Nck1 and -2 prefer composite class ligands of type xPxΦPxxDY, whereas Eps8 SH3 family members can efficiently bind ligands of type ΦPxxDY [17]. Another pair of complexes to compare shows peptides from PAK2 and AIP4 in complex with the SH3 domain of the β-PAK-interactive exchange factor (βPIX) [19,20]. Both peptides utilize the same xP pocket interface of βPIX SH3, but AIP4 binds in Class I whereas PAK2 binds in Class II orientation. Furthermore, AIP4 establishes a canonical PPII conformation and contacts the SH3 through two xP dipeptides, whereas PAK2 is in an extended conformation and makes contacts through xP and Ile-Ala dipeptides [20]. The third pair of complexes illustrating the diversity in ligand binding through the xP-pocket interface shows HPK1 and SLP-76 ligands interacting with the SH3 domain of Mona/GADS [12–14]. Interaction of both peptides with GADS SH3 is driven by an RxxK motif that forms a 3_{10} helical structure and establishes extensive contacts with the negatively charged E/D residues in a manner resembling classical specificity pocket interactions. Leucine at position 47 further complements the binding of the RxxK motif. Both peptides are in Class II orientation, yet in different conformations; HPK1 forms a PPII helix through classical xP dipeptide contacts with the hydrophobic xP pockets of GADS SH3. By contrast, SLP-76 is in an extended conformation and making contacts through an N-terminal xP dipeptide plus an isoleucine. Nevertheless, SLP-76 exhibits 10-fold stronger affinity to GADS SH3 in comparison to HPK1. The lower affinity of GADS SH3 towards PPII-helical ligands (such as HPK1) has been attributed to the orientation of the side chain of its glutamate residue at position 10 [14].

32-residue of the $p47^{phox}$ peptide establishes a helix-turn-helix structure in the specificity zone $p67^{phox}$ SH3. The critical SH3 residues are I50 in β4 strand and V32 in the n-Src loop that make direct contacts with the α-helices in $p47^{phox}$ peptide.

2. Conclusions and perspectives

Here we define non-consensus SH3 ligands as peptides that do not contain a PPII-helical PxxP motif and/or depend on specificity determinants more complex than the canonical basic residue of Class I and II consensus peptides. Instead of an acidic pocket that accommodates such a basic residue, the specificity determinants of non-consensus ligands typically make more extensive contacts with an overlapping but more complex surface in their cognate SH3 domains, which we refer as the specificity zone. Consequently, the binding affinity and selectivity of interactions involving non-consensus SH3 ligands can be substantially greater than observed for consensus peptides. On the other hand, from the distinct and variable nature of such specificity zone contacts, it also follows that non-consensus SH3 ligands cannot be readily predicted from protein sequence data. It is possible that the relative prevalence of non-consensus ligands is significantly higher than currently appreciated, and the perceived dominance of Class I or Class II motifs rather reflects the historical focus on Src-like proteins in studies leading to the identification of the SH3 domain. Indeed, the majority of the approximately 300 SH3 domains encoded by the human genome are still lacking a characterized ligand. The ability to create random peptide libraries of increasing complexity and peptide length, together with an improved capacity to characterize ligand preferences for a large number of different SH3

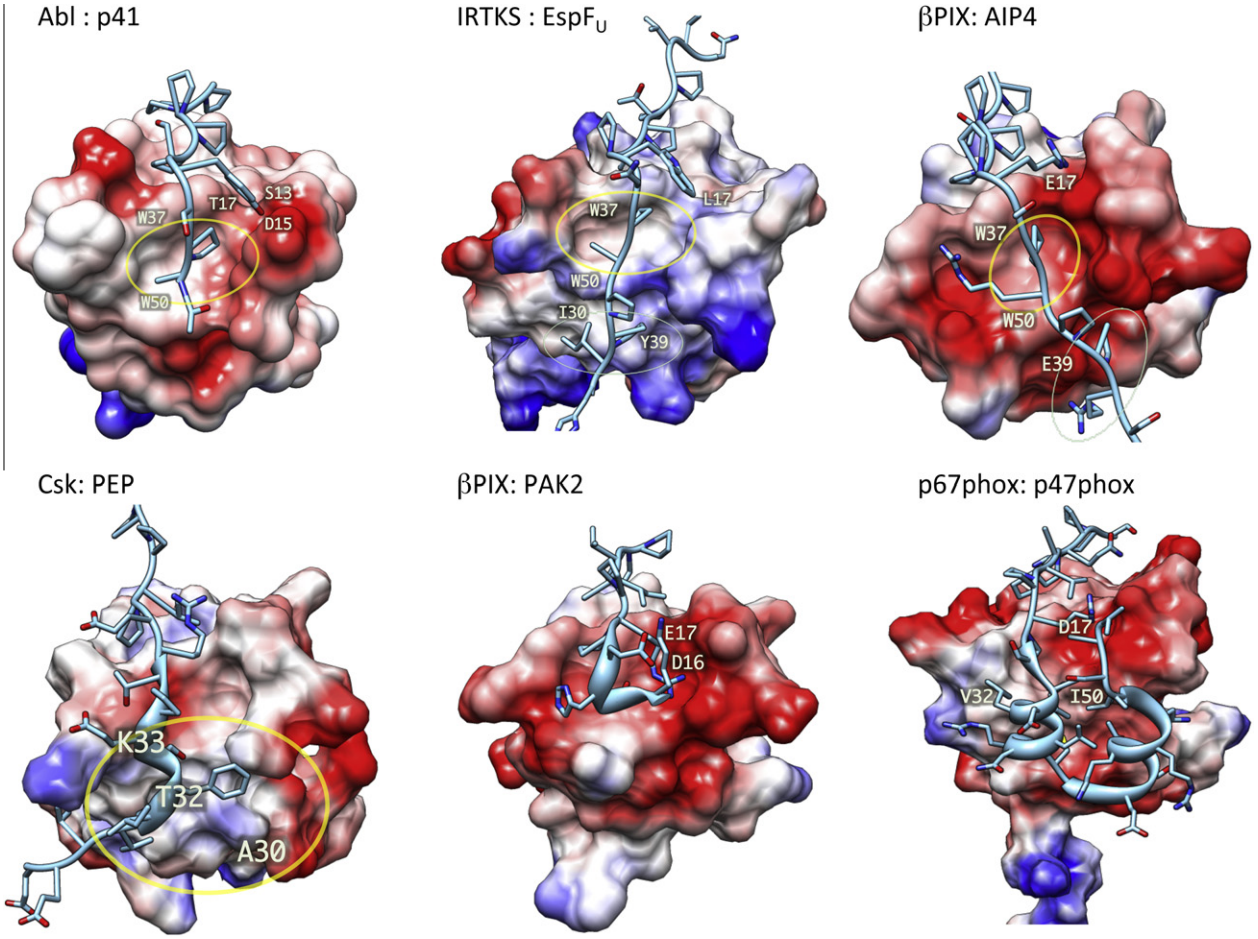


Fig. 4. Anatomy of the specificity zone – ligand interface in selected SH3 domain – peptide complexes. Shown are six different SH3 domains in complex with Class I and II non-consensus peptides to illustrate contacts in the specificity zone that enhance affinity and selectivity of SH3 ligand binding. Insulin receptor tyrosine kinase substrate (IRTKS) SH3 in complex with the pathogen-encoded peptide EspF$_U$ [21], Abelson kinase (Abl) SH3 in complex with p41 [9], and βPIX SH3 in complex with AIP4 peptide [20] all represent Class I interactions (ligand binding in plus-orientation), but their binding preferences are very different. In IRTKS and Abl, the canonical acidic residue at position 17 is replaced by leucine and threonine, respectively, compromising their binding to classical RxxPxxP ligands, whereas βPIX contains a glutamate at position 17, and accordingly accommodates a typical basic ligand residue in this slot. However, the specificity zones in Abl, βPIX and IRTKS contain additional slots for enhanced ligand binding specificity and affinity. In all these three SH3 domains the first additional binding pocket (circled in yellow) is hydrophobic and is established by the highly conserved W37 residue together with W50 from β4 strand. This pocket interacts with a proline residue in the ligand. The second additional pocket found in IRTKS and βPIX (circled in green) helps to further increase their ligand binding specificity. Hydrophobic residues rarely encountered at the tip of β2 strand and in β3 strand (positions 30 and 39) render this second pocket in IRTKS highly hydrophobic, and strongly favors docking of an IP dipeptide. Thus, through the combined action of the two hydrophobic pockets in the specificity zone and the two canonical xP pockets IRTKS specifically recognizes peptide ligands with the consensus IPxXPxxxXPxXP [21]. By contrast in βPIX the position 39 contributing to the second specificity zone pocket is negatively charged by glutamate, and accommodates a positively charged arginine of the AIP4 peptide [20]. Nevertheless, as already discussed in the case of xP pocket usage in Fig. 3, βPIX SH3 binds also non-consensus Class II ligands, and forms 3_{10} helix upon interaction with the specificity zone, as highlighted for βPIX SH3 – PAK2 complex [19].

domains using modern high-throughput technologies may soon shed more light into this question (see [26–28]). Finally, while mediating tight and specific contacts with SH3 ligands, the complex and variable surface of the specificity zone also has much more potential for drug targeting than the flat, hydrophobic, and structurally conserved xP pockets. Therefore, the specificity zone should be considered a prime target in the efforts to develop pharmacological inhibitors against disease processes mediated by SH3 domain–guided protein interactions.

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